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L3: Entry 2 of 25

File: USPT

May 11, 2004

DOCUMENT-IDENTIFIER: US 6733777 B2

TITLE: Cationic reagents of transfection

Brief Summary Text (33):

In a preferred embodiment of this invention, the neutral lipid is DOPE. A co-lipid according to the present invention is a compound capable, alone or in combination, with other lipid components, to form a stable liposome, including but not limited to co-lipids selected from the following group: phospholipid-like compounds, such as lecithine, phosphatidylcholine, dioleoyl-phosphatidylcholine (DOPC), phosphatidylethanolamine (PE), phosphatidylserine, phosphatidylglycerine, phosphatidylinositol, sphingomyeline, cephaline, cardiolipine, phosphatidic acid, cereoroside, diacetylphosphate, lysophosphatidylethanolamine, dipalmitoylphosphatidylcholine, dioleoylphosphatidylglycerol, dipalmitoylphosphatidylglycerol, palmitoyl-oleoylphosphatidylcholine, palmitoyl-oleoylphosphatidylethanolamine, diheptadecanoylphosphatidylethanolamine, dilauroylphosphatidylethanolamine, dimyristoylphosphatidylethanolamine, distearoylphosphatidylethanolamine, beta-linoleoyl-gamma-palmitoylphosphatidylethanolamine and beta-oleoyl-gamma-palmitoylphosphatidylethanolamine and the like, lipids not containing phosphorous, including but not limited to steroids, terpenes, stearylamine, dodecylamine, hexadecylamine, acetylpalmitate, glycerinericine-oleate, hexadecylstearate, isopropylmyristate, dioctadecyl-ammoniumbromide, amphoteric polymeres, such as triethanoleamine-laurylsulfate, lysolecithin, and similar compounds.

Current US Original Classification (1):

424/450

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L3: Entry 3 of 25

File: USPT

Oct 1, 2002

DOCUMENT-IDENTIFIER: US 6458381 B1

**\*\* See image for Certificate of Correction \*\***

TITLE: Lipids and their use, for example, in liposomes

Brief Summary Text (31):

An optional co-lipid is to be understood as a compound capable of producing a stable liposome, either alone, or in combination with other lipid components. Examples of optional co-lipids are phospholipid-related materials, such as lecithin, phosphatidylcholine, dioleoylphosphatidylcholine (DOPC), phosphatidylethanolamine (PE), phosphatidylserine, phosphatidylglycerol, phosphatidylinositol, sphingomyelin, cephalin, cardiolipin, phosphatic acid, cerebrosides, dicetylphosphate, etc., non-phosphorous lipids like steroids and terpenes. Additional non-phosphorous lipids are, e. g. stearylamine, dodecylamine, hexadecylamine, acetylpalmitate, glycerol ricinoleate, hexadecyl stearate, isopropyl myristate, dioctadecylammonium bromide, amphoteric polymers, triethanolamine lauryl sulfate, cationic lipids described before and the like.

Current US Original Classification (1):

424/450

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L12: Entry 6 of 6

File: USPT

Jun 26, 2001

DOCUMENT-IDENTIFIER: US 6251433 B1

TITLE: Polycationic polymers

Detailed Description Text (148):

Cationic liposomes are readily available. For example, N[1-2,3-dioleyloxy)propyl]-N,N,N-triethylammonium (DOTMA) liposomes are available under the product line Lipofectin.RTM., from GIBCO BRL, Grand Island, N.Y. (See, also, Felgner et al., 1987, Proc. Natl. Acad. Sci. USA 84:7413-7416). Other commercially available liposomes include transfectace (DDAB/DOPE) and DOTAP/DOPE (Boehringer). Other cationic liposomes can be prepared from readily available materials using techniques well known in the art. See, e.g., Szoka et al., 1978, Proc. Natl. Acad. Sci. USA 75:4194-4198; PCT Publication No. WO 90/11092 for a description of the synthesis of DOTAP (1,2-bis(oleoyloxy)-3-(trimethylammonio)propane) liposomes.

Detailed Description Text (179):

Preferably, the isoelectric point of the instant polycationic agents to neutralize nucleic acids is at least 9.

Detailed Description Text (241):

Typically, the polycationic agents exhibit a predicted isoelectric point of at least 9, excluding the terminal groups. Further, the agents contain, excluding the terminal groups, at least 20% positively charged monomers; more typically, at least 25%; more typically, 30%; and preferably, at least 33% positively charged monomers. Typically, the agents do not comprise greater than 5% acidic monomers and preferably none.

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File: USPT

Mar 1, 1994

DOCUMENT-IDENTIFIER: US 5290563 A

TITLE: Method for combining a mixture of heterogeneous substances with liposomes

Abstract Text (1):

In the method for combining with liposomes heterogeneous substances contained in a mixture, in particular, allergenic substances such as allergens and/or allergenic extracts, contained in an allergenic preparation, by adsorption on the surface of, and/or incorporation in, liposomes which comprise cholesterol, a phospholipid and/or at least one ionic lipid which gives the liposome a positive or negative charge, the liposome or its constituents are combined with the mixture of heterogeneous substances, the pH of the entire combination being higher or lower than the isoelectric point ip of the substances contained in the mixture, depending on whether the ionic lipid is charged positively or negatively respectively.

Detailed Description Text (1):

The object of the present invention is a method of the type described at the beginning in which liposomes are made up of cholesterol, a phospholipid and/or at least one ionic lipid which gives the liposome a positive or negative charge. This method is characterized in that the liposome or its constituents are combined with the mixtures of heterogeneous substances, the pH of the whole being higher or lower than the isoelectric point ip of the substances contained in the mixture, depending on whether the ionic lipid is positively or negatively charged respectively.

Detailed Description Text (53):

Table II, which follows, combines the results obtained in the case where the pH of the liposome-allergen mixture is higher than the isoelectric point (ip) of the allergens (which is often the case when following Bangham's method) and in the case where the pH is reduced, for example, with a solution of HCl 0, 1N, to a final value lower than the ip of the allergens, the ionic lipid used being DCP (negative charge).

## CLAIMS:

1. A method of combining protidic allergens and/or allergenic extracts selected from the group consisting of natural allergens from animal or vegetable origin, allergenic proteins and peptides, with a negatively or positively charged liposome comprised of cholesterol, a phospholipid and/or at least one ionic lipid which gives the liposome a positive or negative charge, comprising
  - a) determining the isoelectric point ip of one or more of the allergenic substances to be mixed and
  - b) mixing said allergenic substance or substances with said liposome at a pH lower than said isoelectric point when the liposome is negatively charged or at a pH higher than said isoelectric point when said liposome is positively charged.
2. A method according to claim 1 wherein the liposome is positively charged and the weakest isoelectric point of said substance is determined.
3. A method according to claim 1 wherein the liposome is negatively charged and the

strongest isoelectric point of said substance is determined.

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File: USPT

Nov 12, 1991

DOCUMENT-IDENTIFIER: US 5064655 A

TITLE: Liposome gel composition and method

Abstract Text (1):

A liposome gel composition and method of preparing the same. The composition is composed of charged liposomes, at a relatively low lipid concentration, in a low-conductivity medium. The composition preferably contains a zwitterionic compound at its isoelectric point. The liposomes can be designed for cosmetic use, transdermal drug delivery, or enhanced retention on mucosal tissues, such as for ophthalmic use.

Brief Summary Text (19):

The invention also includes a high-viscosity liposome gel composition formed of a suspension of charged liposomes in a low-conductivity aqueous suspension medium. According to an important aspect of the composition, the aqueous medium has a selected pH between 3.5 and 10.5, and preferably between about 5.5 and 8.5, and contains a zwitterionic compound, such as an amino acid, whose isoelectric point is within the pH specified range. The zwitterionic compound allows the viscosity of the composition to be selectively varied by adjusting the pH of the medium.

Brief Summary Text (22):

The lipids may be added directly to a low-conductivity aqueous medium or, alternatively, may be added to an aqueous medium containing a zwitterionic compound whose isoelectric point is substantially different from that of the pH of the medium (such that the medium has relatively high conductivity). Following formation of a fluidic liposome suspension, the medium is titrated to a pH at which the zwitterionic compound is at its isoelectric point, yielding a low-conductivity condition which results in gel formation in the suspension. The liposome suspension may be more easily sized, freed of non-liposome-bound drug, filter-sterilized or otherwise processed in the more fluidic state prior to gelling.

Detailed Description Text (37):

As will be discussed in Section D below, the aqueous medium may initially be adjusted to a pH at which the zwitterionic compound is substantially in a charged form, so that the medium has a relatively high electrolyte concentration, i.e., a relatively high conductivity. By adjusting the pH to the isoelectric point of the zwitterionic compound, typically after lipid hydration and liposome formation, the compound becomes non-electrolytic, liposome formation, the compound becomes non-electrolytic, i.e., has the desired low conductivity.

Detailed Description Text (50):

After liposome processing, the non-viscous liposome suspension is converted to the desired gel form by titrating the pH of the suspension to a isoelectric point of the zwitterionic species. As mentioned above, the titration must be carried out without significantly increasing the concentration of dissociable salts in the medium. This can be done by titrating with acids or bases which produce volatile salt components, such as certain ammonium salts, or which produce insoluble salts. Preferably, the titration is done by forming an initial liposome suspension in a medium containing low zwitterionic concentration, then titrating with a concentrated solution of the same zwitterionic compound, until the desired pH is



reached, as detailed in Example 3.

CLAIMS:

29. The method of claim 28, wherein said mixing includes adding the lipid composition to an aqueous medium whose pH is substantially different from the isoelectric point of the zwitterionic compound, thereby to form a fluid non-gel liposome suspension, and adjusting the pH of the suspension to the isoelectric point of the zwitterionic compound, to produce the desired gel suspension.

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File: EPAB

Jan 30, 1991

DOCUMENT-IDENTIFIER: EP 410848 A1

TITLE: Process for combining a mixture of heterogeneous substances with liposomes.

Abstract Text (1):

In the process for combining heterogeneous substances, contained in a mixture, with liposomes, in particular allergenic substances, such as allergens and/or allergenic extracts, contained in an allergenic preparation, by adsorption at the surface of and/or incorporation in liposomes, which contain cholesterol, a phospholipid and/or at least one ionic lipid which confers a positive or negative charge on the liposome, the mixture of heterogeneous substances is brought into contact with the liposome or its constituents, the pH of the whole being above or below the isoelectric point pI of the substances contained in the mixture, depending on whether the ionic lipid is positively or negatively charged, respectively.

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